

Effects of sleep disruption on mood and pain: Role of inflammation

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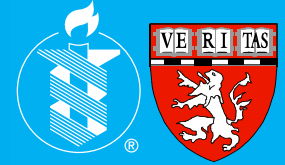
Harvard Medical School

Beth Israel Deaconess Medical Center

Boston, MA

- **Sleep deficiency affecting mood/emotional well-being**
- **Sleep deficiency affecting pain/physical well-being**
- **Role of inflammation in the association between sleep deficiency and pain**

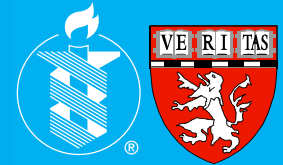
Sleep deficiency affecting mood/emotional well-being



Population-based/clinical studies

- ➔ Individuals with **irregular sleep-wake patterns**, such as shift workers, pilots, medical emergency staff have increased rates of depression and anxiety (*Bannai & Tamakoshi, review 2014*).
- ➔ Individuals with **insomnia** have an increased risk of developing a mood disorder, such as depression or anxiety (*Weissmann et al., 1997; Neckelmann et al., 2007; Baglioni et al., 2010*).

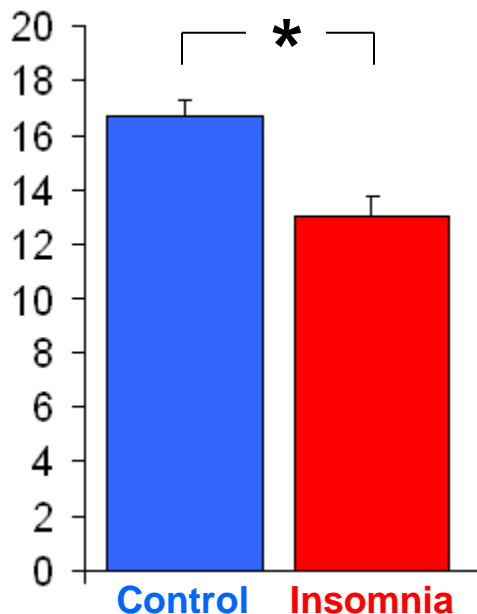
Insomnia affecting mood/well-being



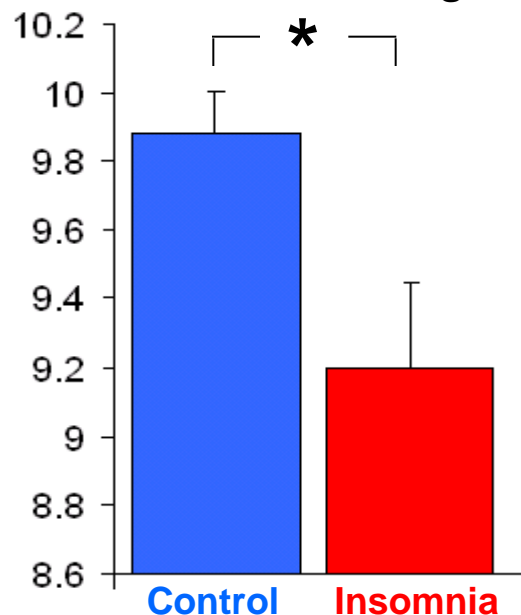
Well-being in insomnia without psychiatric comorbidities

Insomnia disorder N=17 (22.6 ± 0.9 yrs, 11 women), individually matched with healthy participants.

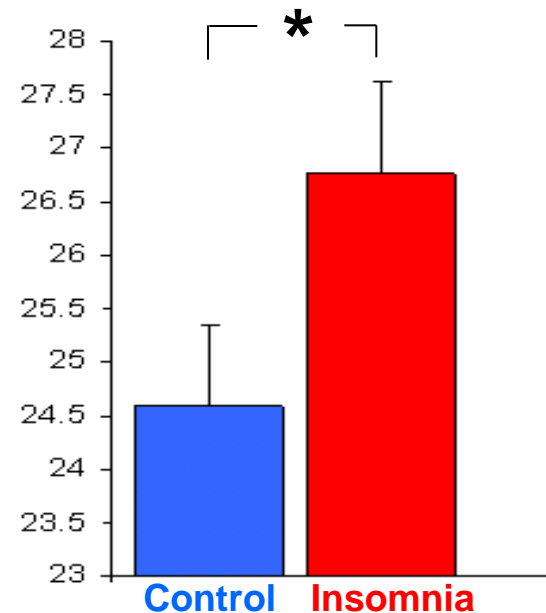
SF36
Emotional Functioning



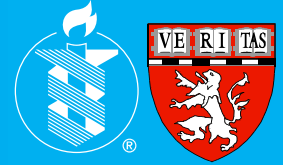
SF36
Social Functioning



PSS14
Perceived Stress



Experimental sleep deficiency affecting mood/well-being



Experimental studies

General experimental setting

Healthy participants, without history of mood- or pain-related disorders

Manipulation of sleep in form of

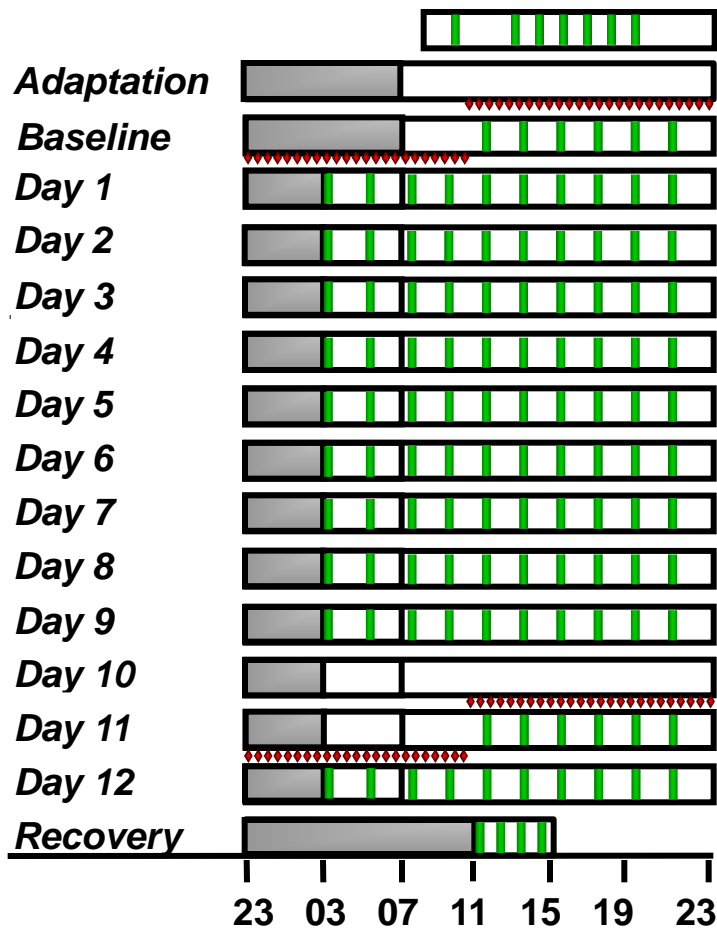
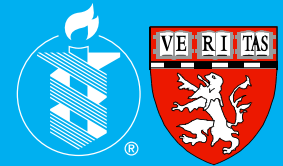
- Total sleep deprivation of up to 3 days
- Sleep restriction or fragmentation of up to 14 days
- Repeated episodes of sleep restriction and sleep recovery of up to one month

Controlled in-laboratory conditions

Assessment of:

- mood via questionnaires/rating scales
- affective response to emotion induction

Mood/emotional well-being in response to experimental sleep restriction

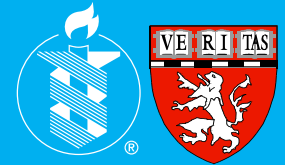


Protocol

- Healthy participants (21-40 years) without a history of sleep, mood or pain-related disorder
- Randomized to:
4h of sleep/night for 12 days (23-03h, N=22) or
8h of sleep/night for 12 days (23-07h, N=18)
- Assessment of mood and pain through computerized visual analog scales (VAS) presented every 2 hours throughout protocol
- 24h blood and urine collection at baseline and 10th day of partial sleep deprivation



Mood/emotional well-being in response to experimental sleep restriction



Study/Environmental Controls



Food: Calorie- and electrolyte-balanced diets; meals served at standard times.

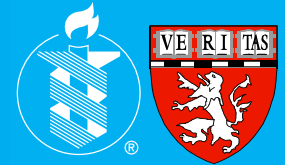
Fluids: No caffeine.

Body position: In bed in a semi-supine position from 03:00 to 07:00h in sleep restriction condition; lights dimmed to <40 Lux.

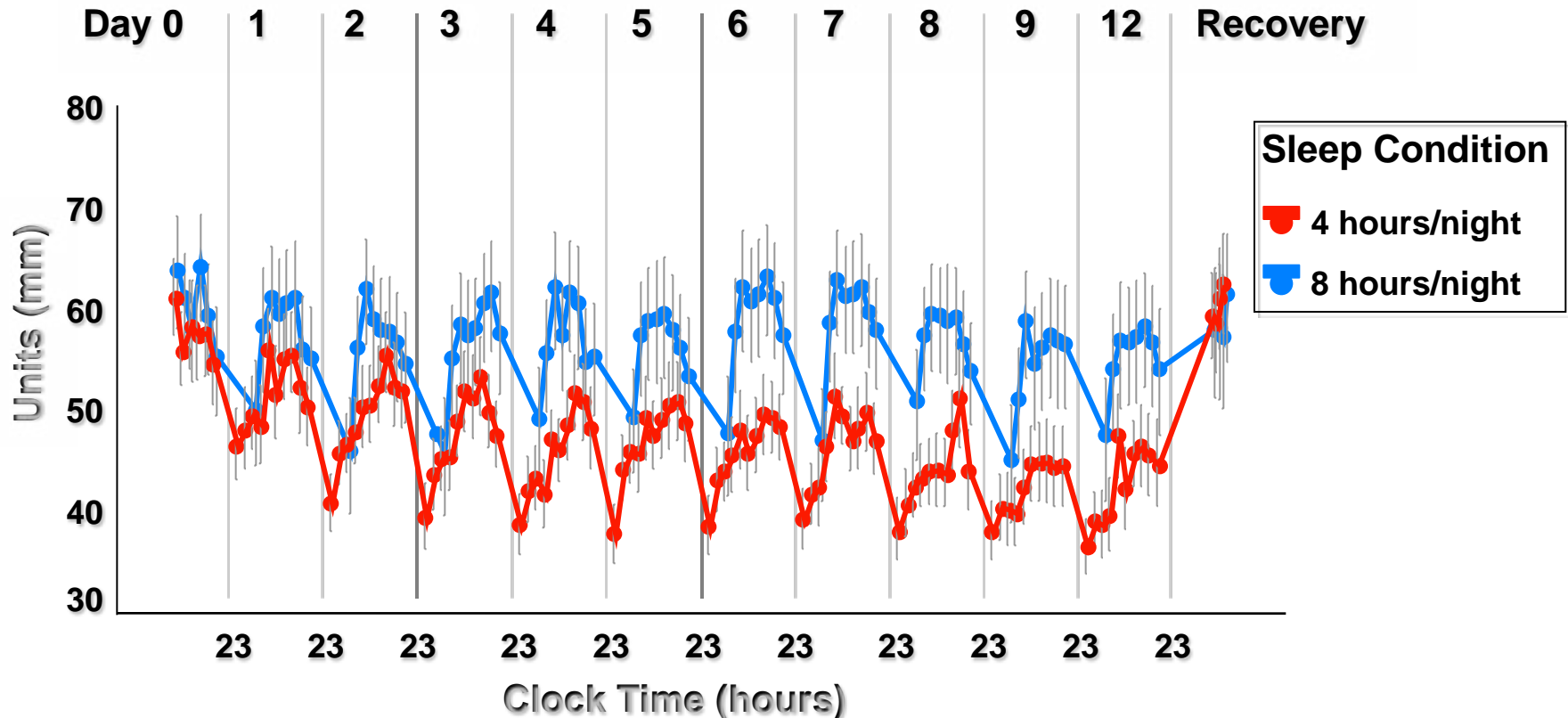
Motor activity: Hourly walks, continuation of habitual gym routine.

Social: Research monitor with participants during all waking periods. Access to email/phone. Visits of friends/family.

Mood/emotional well-being in response to experimental sleep restriction

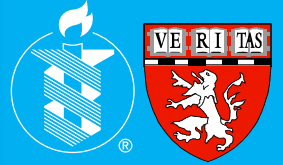


Optimism- Sociability



Prolonged sleep restriction progressively deteriorates positive outlook and social functioning.

Sleep deficiency and pain



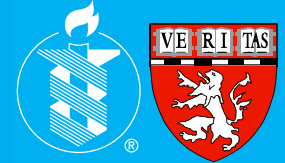
- Association between pain and sleep was first mentioned in the Gilgamesh Epic (1900 BC): In Search of Immortality

***"...my face was not sated with sweet sleep,
I fretted myself with wakefulness;
I filled my joints with aches."***

*Translation by E.A. Speiser,
in Ancient Near East Texts (Princeton, 1950)*



Sleep deficiency ↔ pain



Clinical/Population-based studies

Pain reporting → **Sleep deficiency**

Fibromyalgia (*Affleck et al., 1996*)

Migraine & other primary headache disorders (*rev. Alberti 2006*)

Surgery (*Closs et al., 1992*)

General population (*Edwards et al., 2008*)

Sleep deficiency → **Pain reporting**

Chronic widespread pain (*Davies et al., 2008*)

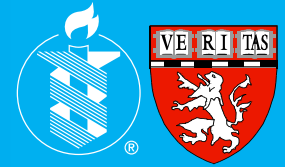
Migraine (*Rains & Penzien 1996*)

Surgery (*Wright et al., 2009*)

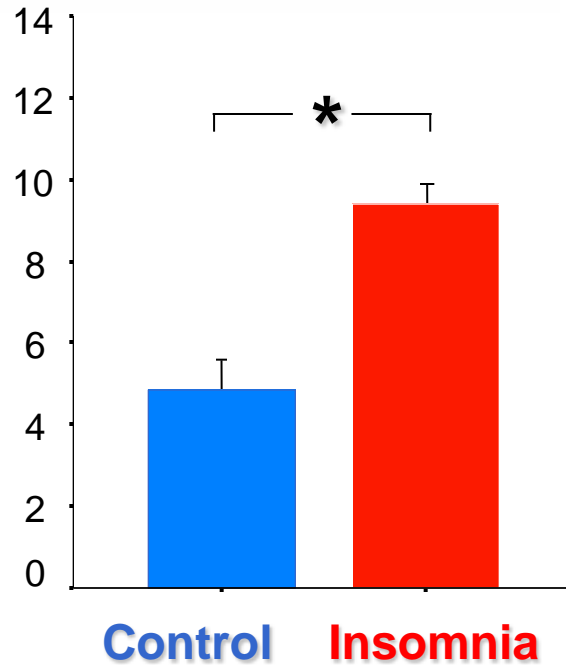
Temporomandibular disorders (TMD) (*Quartana et al., 2010*)

General population (*Edwards et al., 2008*)

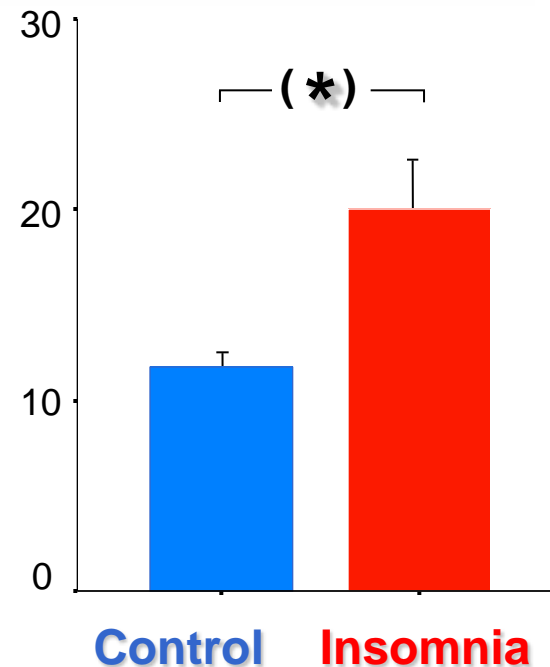
Spontaneous pain in Insomnia disorder (without comorbidities)



Pain Frequency (days)

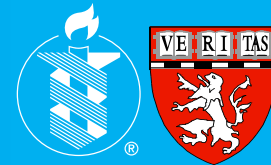


Pain Intensity (units)

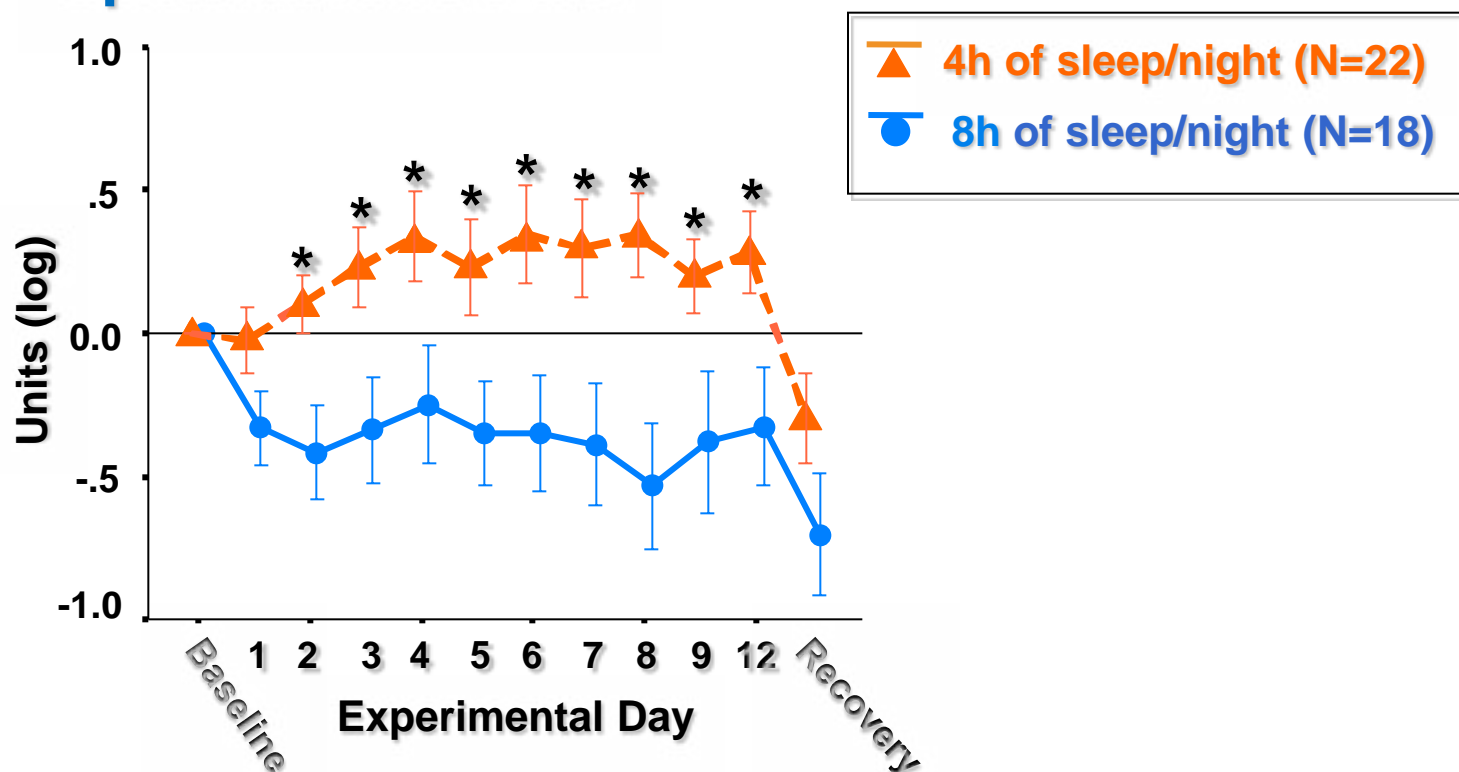


Individuals with insomnia disorder report pain on twice as many days as healthy controls.

Spontaneous pain in response to experimental sleep restriction

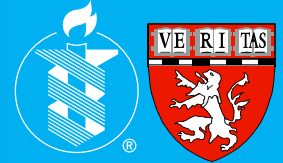


Spontaneous Pain



Prolonged insufficient sleep leads to an increase of spontaneous pain in a young, healthy population.

Evoked pain in response to sleep deficiency



VOL. III. No. 5.

SEPTEMBER, 1896.

THE PSYCHOLOGICAL REVIEW.

STUDIES FROM THE PSYCHOLOGICAL LABORATORY OF THE UNIVERSITY OF IOWA.

ON THE EFFECTS OF LOSS OF SLEEP.¹

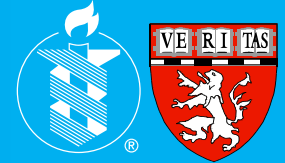
BY PROFESSOR G. T. W. PATRICK AND DR. J. ALLEN GILBERT.

Pain threshold to pressure decreased in the course of 90 hours of total sleep deprivation. N=1.

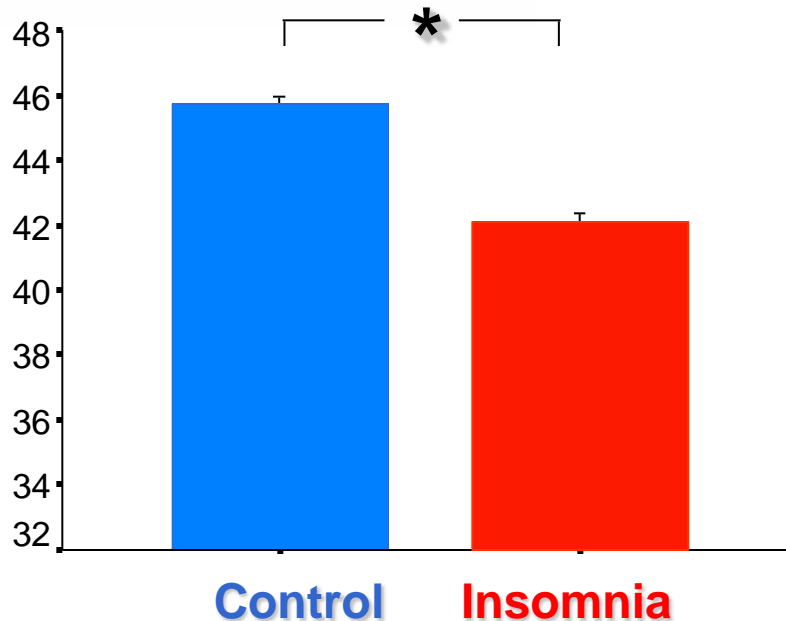
To date, numerous studies have shown that...

Experimental sleep deficiency, either in form of total sleep deprivation, selective sleep stage deprivation, sleep restriction, or sleep fragmentation leads to a decrease in pain thresholds.

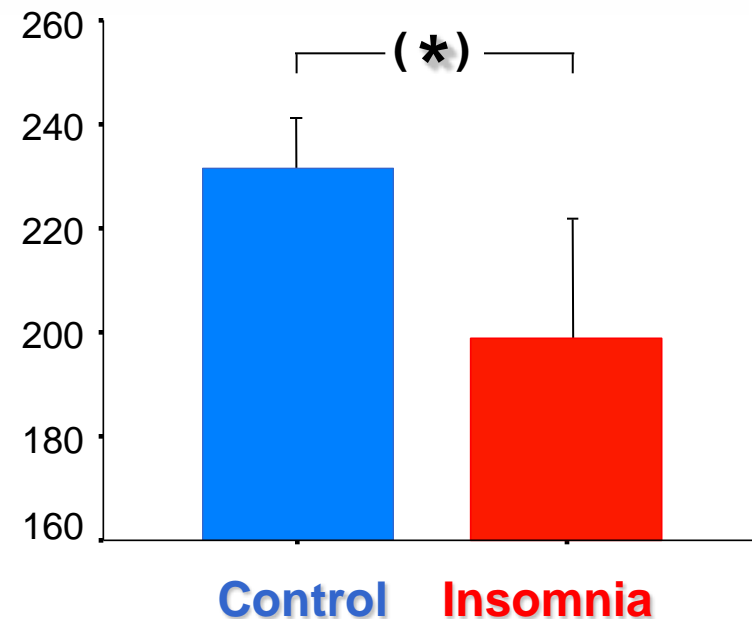
Pain thresholds in insomnia disorder



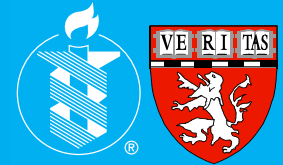
Heat Pain Threshold (°C)



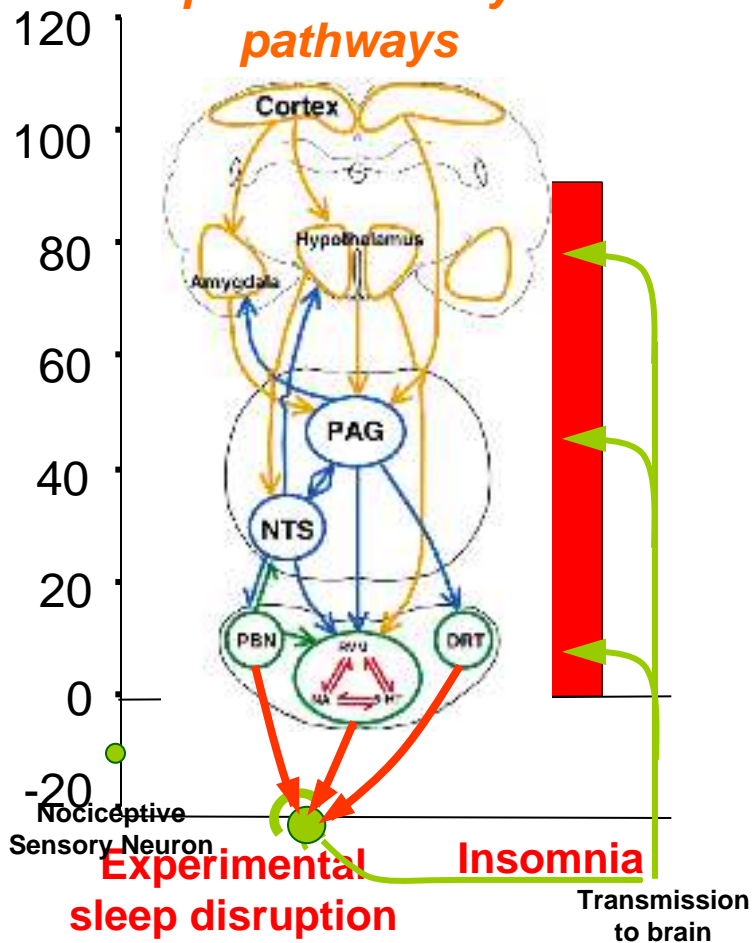
Pressure Pain Threshold (kPa)



Pain inhibition in experimental sleep disruption and insomnia



% Deterioration of **Descending pain inhibitory pathways**



Adapted from Millan, 2002

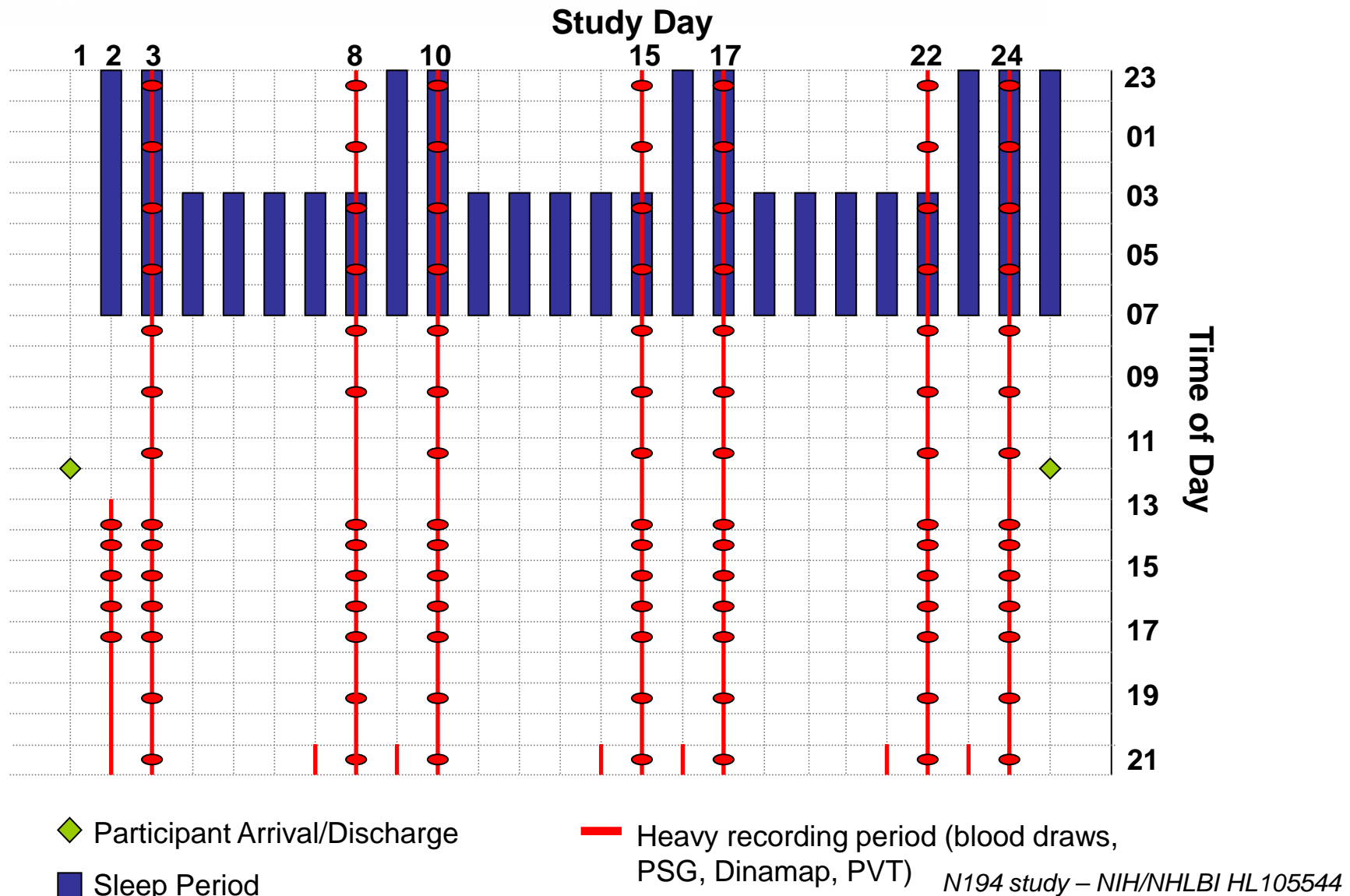
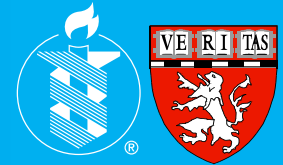


Capacity to inhibit pain assessed by **Conditioned Pain Modulation** Paradigm (CPM).

Pain inhibition is deteriorated in **experimental sleep disruption** over 3 nights (*graphical estimation from Smith et al., 2007*).

Pain inhibition is even more deteriorated in **insomnia disorder** (*Haack et al., 2012; data expressed as % change from respective control levels*).

Repeated exposure to patterns of sleep restriction & recovery - Protocol

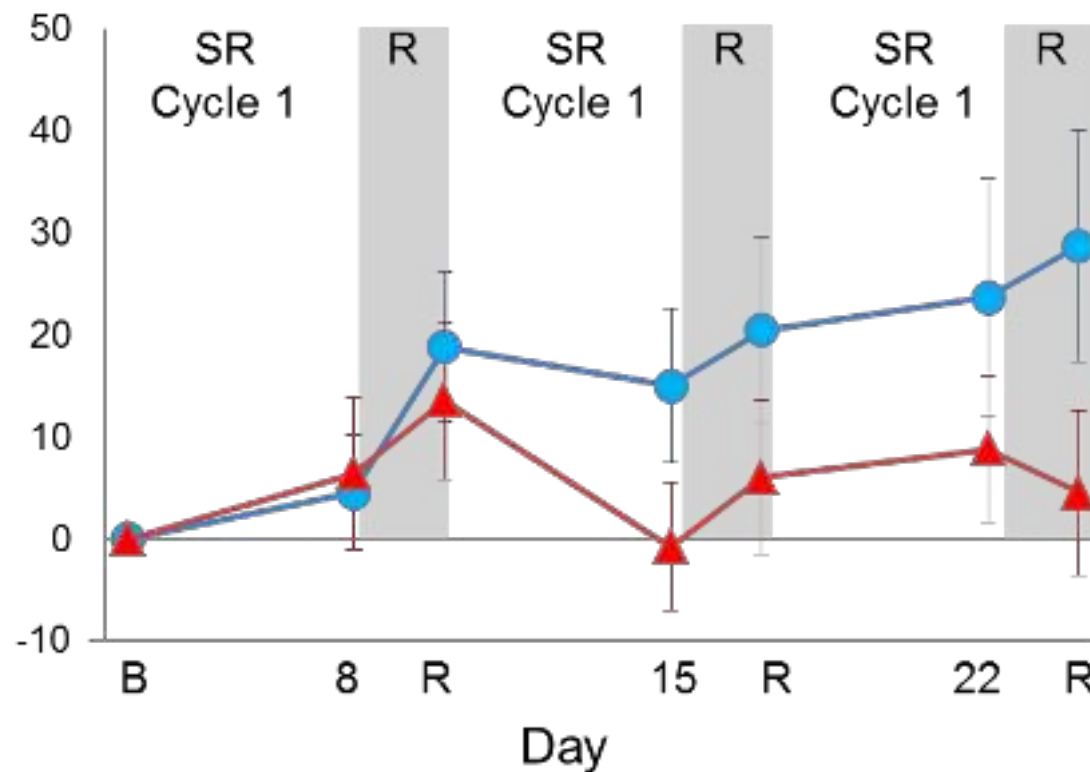


Habituation to pain in response to repeated patterns of sleep restriction & recovery



Habituation to cold pain

Cold pressor test (CPT), change from baseline (sec)



- ▲ Repeated cycles of sleep restriction and recovery
- Control (8 hours/night for 25 days)

SR = Sleep restriction
B = Baseline;
R = Recovery

Habituation to stressors or other challenges is a key feature of many biological systems, but when undergoing repeated exposure to sleep restriction, the ability to habituate to cold pain is deteriorated.

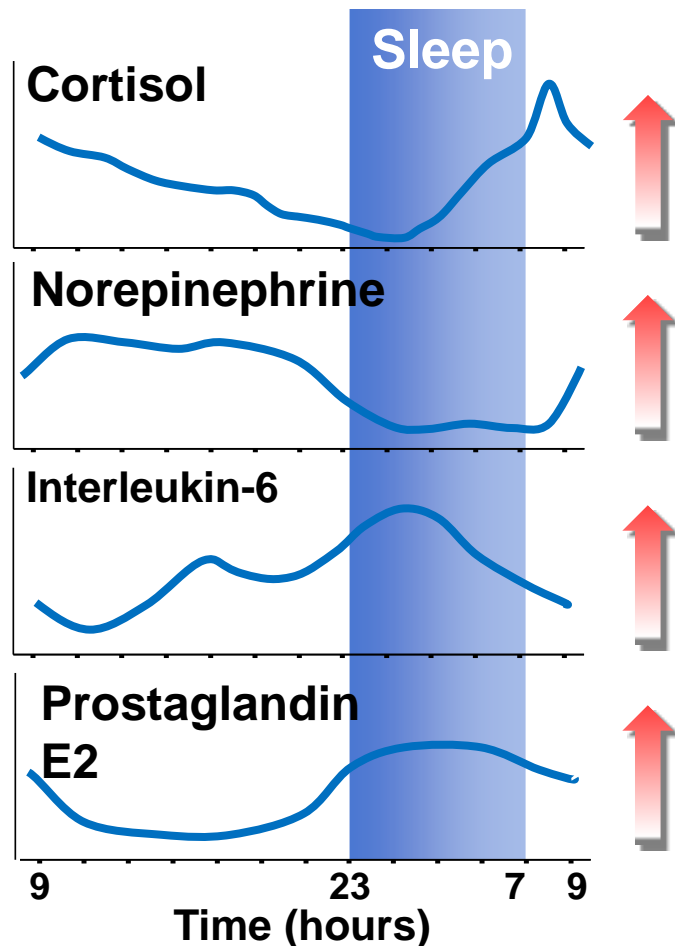
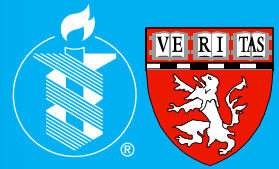
Spontaneous and evoked pain in response to sleep deficiency - Summary



- ➔ Any form of sleep deficiency – total sleep deprivation, sleep restriction, sleep disruption, insomnia symptoms or disorder, appears to amplify **spontaneous pain reporting**.
- ➔ Experimental sleep restriction, sleep disruption, or insomnia disorder is associated with
 - **decreased pain thresholds**
 - **decreased pain inhibition**
 - **decreased habituation to pain**

? Mechanisms ?

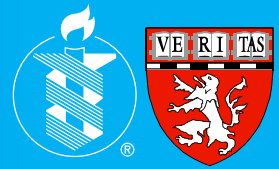
Rhythms affected by the sleep-wake cycle



Sleep has a regulatory influence on all major physiological systems.

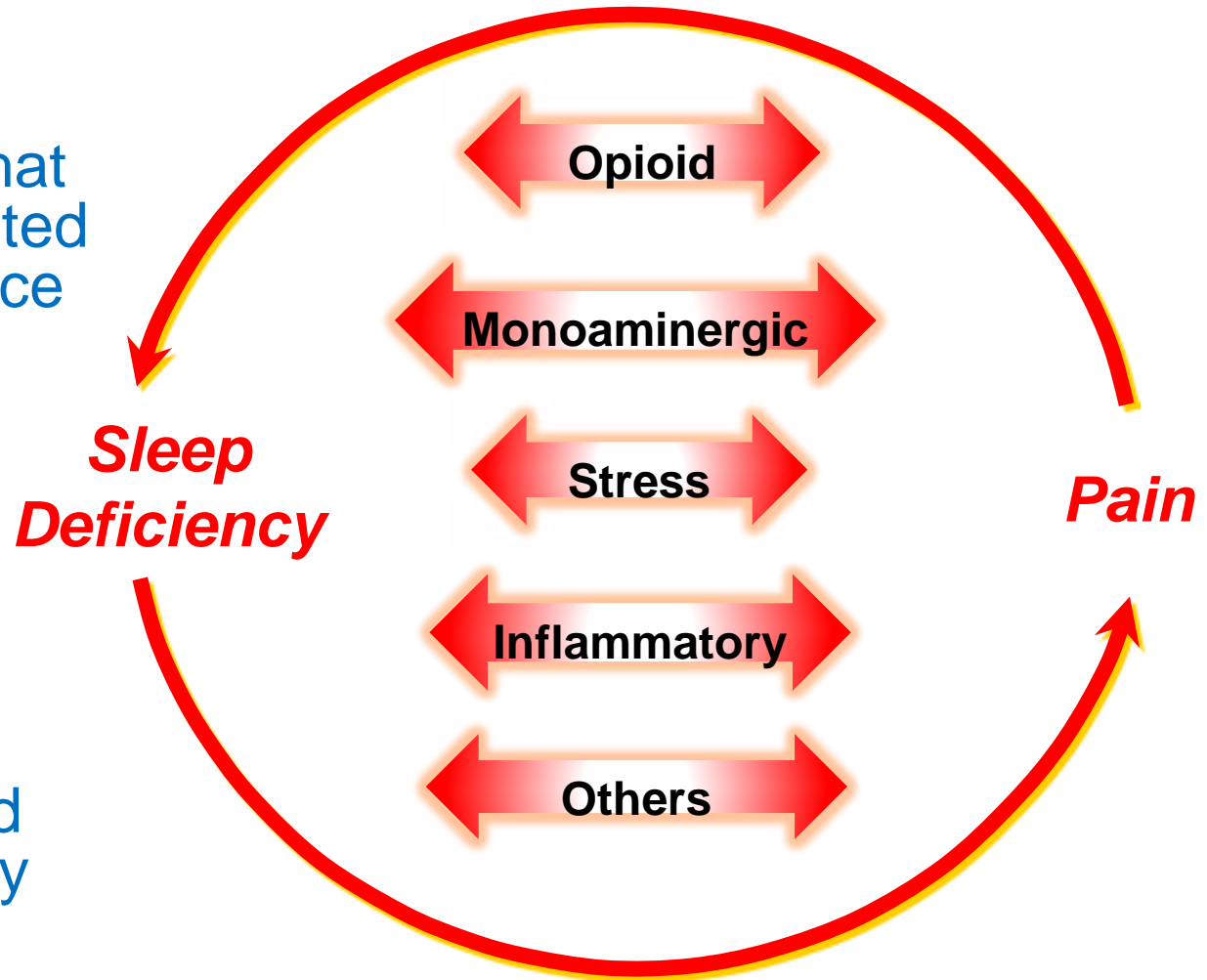
➔ Without sufficient and good quality sleep, rhythms of all major physiological systems are dysregulated or displaced.

Systems affected by both sleep and pain?



Various systems that become dysregulated by sleep disturbance do also affect pain processing.

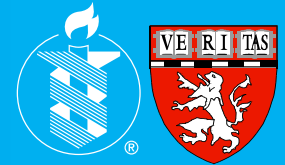
Vice versa, pain affects various systems that are necessary for good quantity and quality sleep.





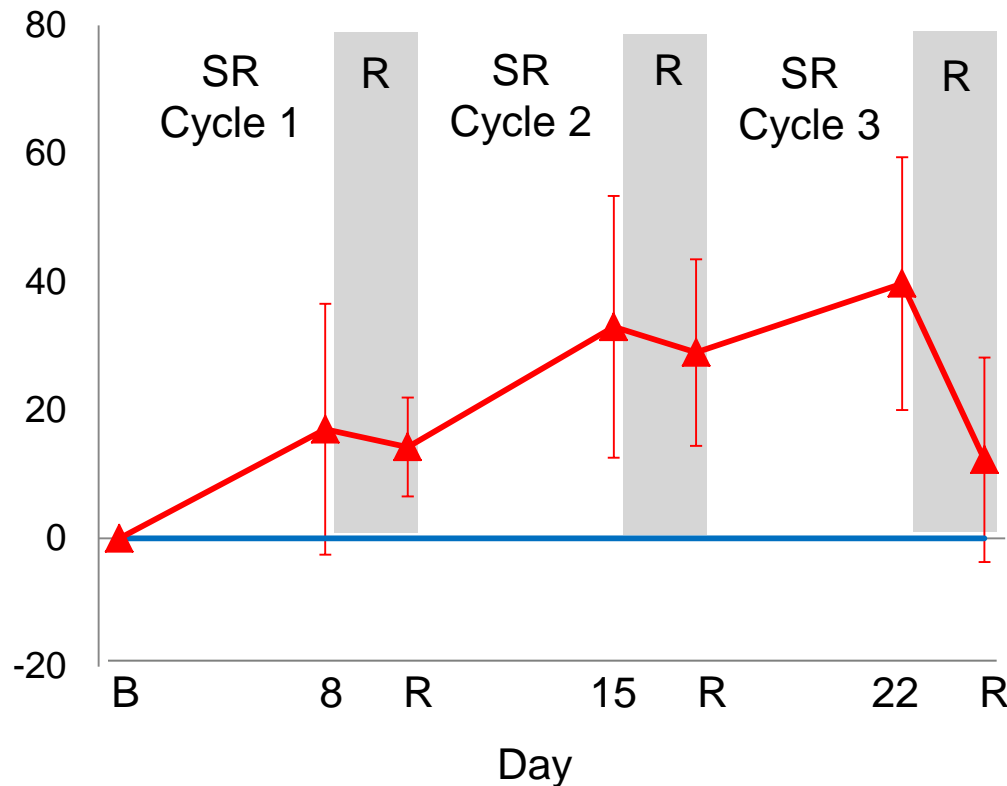
Inflammation
as a mechanistic pathway
inter-connecting sleep and pain?

Inflammatory response to repeated patterns of sleep restriction & recovery



IL-6 positive monocytes

(% Change from Control Sleep [8h/night for 25 days])

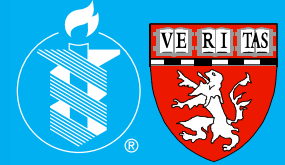


▲ Repeated cycles of sleep restriction and recovery

SR = Sleep restriction
B = Baseline;
R = Recovery

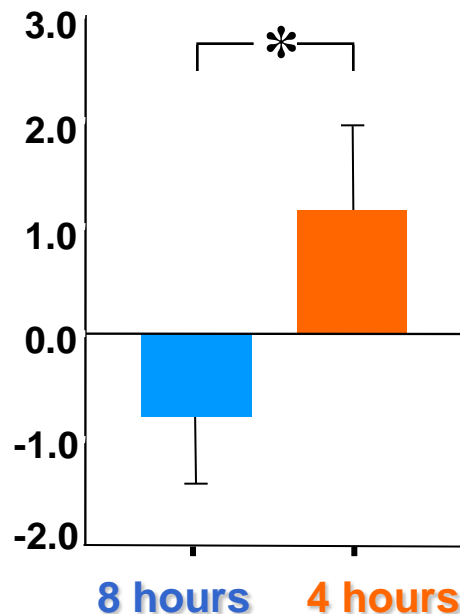
➡ Inflammatory markers increase across repeated episodes of sleep restriction, and do not return to baseline after a couple of nights with full sleep.

Inflammatory and pain responses to experimental sleep restriction

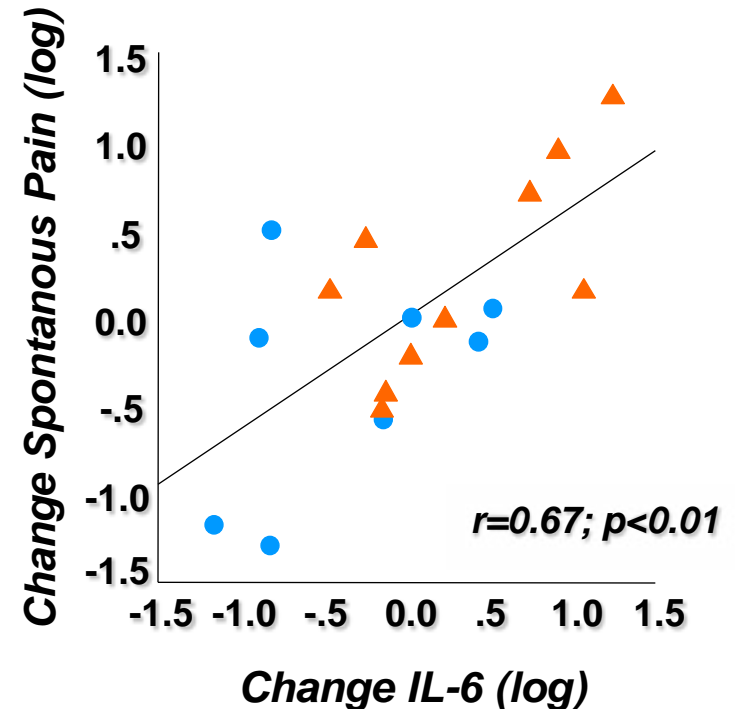
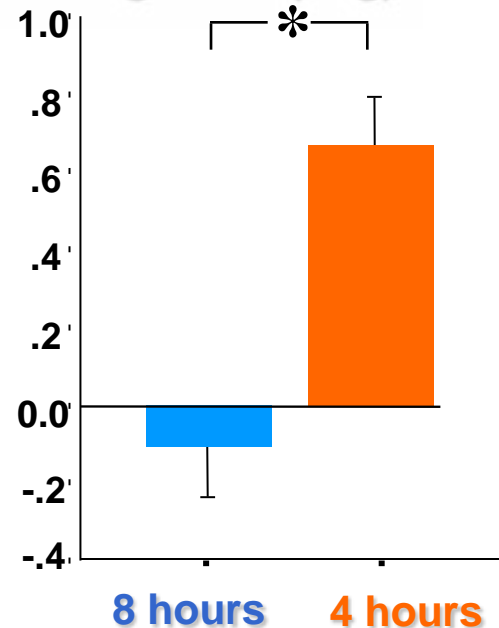


▲ 4h of sleep/night for 10 nights ● 8h of sleep/night for 10 nights

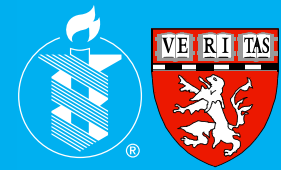
Change IL-6 (pg/ml)



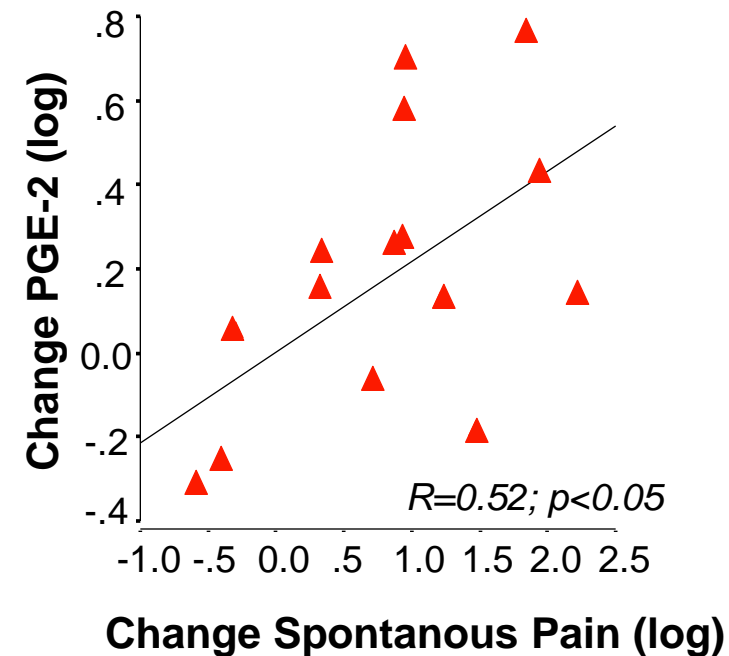
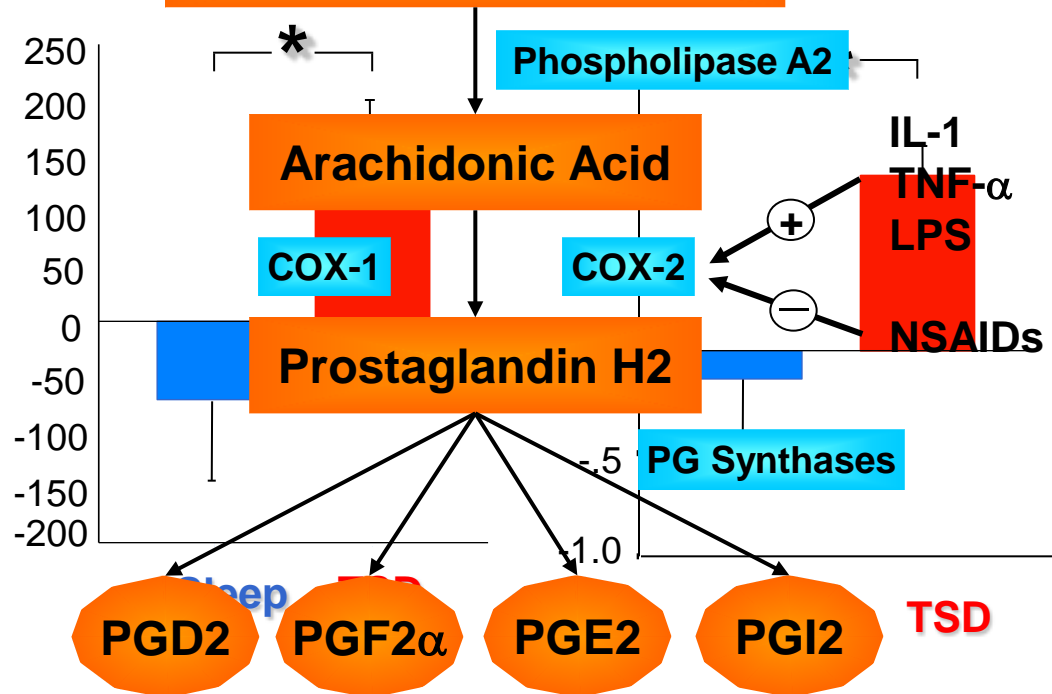
Change Pain (Log)



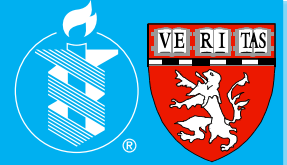
Prostaglandin E2 in response to total sleep deprivation (TSD over 3 days)



Change in PGE_2 and spontaneous pain
metabolites



Overall Summary

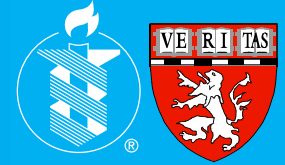


- ➡ Sleep deficiency, as it occurs in the experimental or natural environment, leads to facilitation or development of
 - spontaneous pain.
 - enhanced sensitivity to evoked pain.
 - decreased capacity to inhibit pain and to habituate to pain.

- ➡ **Inflammatory mediators**, such as IL-6 and PGE2, appear to play a mediating role in the effects of sleep deficiency and pain. Causation still needs to be established.

- ➡ Identification of and targeting mechanisms important to reduce pain exacerbated by sleep deficiency.

Acknowledgement



Janet Mullington, PhD
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Huan Yang, PhD
Daniel Cohen, MD

Renata Surette, BS
Vrushank Bhatt, MS

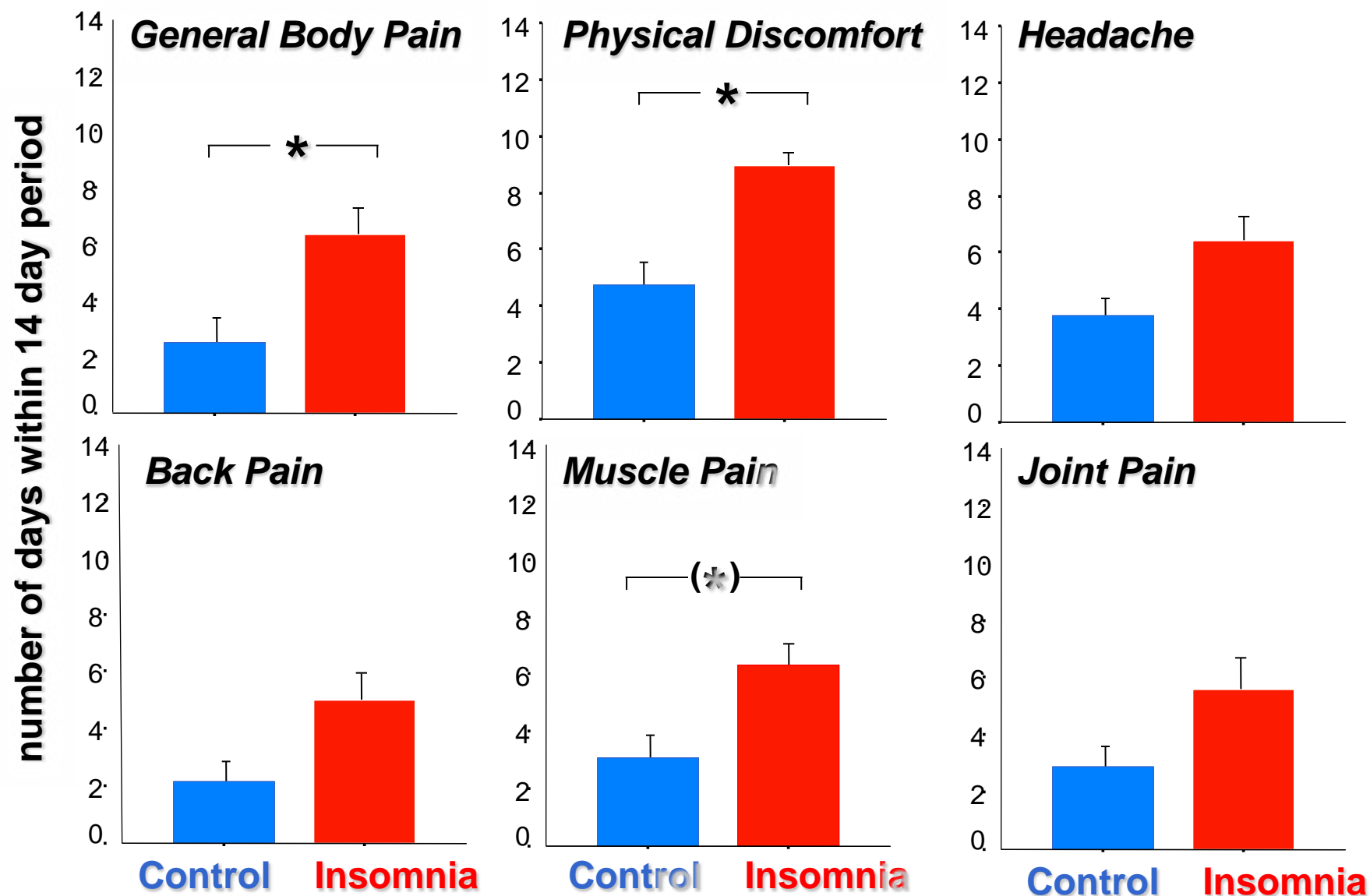
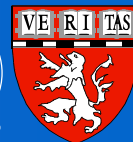
Clinical Research Center

Support:

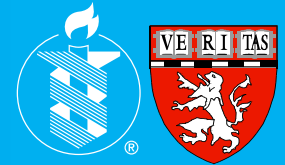
*NIH/NIMH/NIA/NHLBI grants: MH60641
(JMM), HL75501 (JMM), HL106782 (JMM),
HL105544 (MH), RR 01032 (BIDMC CRC)
Sleep Research Society Foundation (MH)*



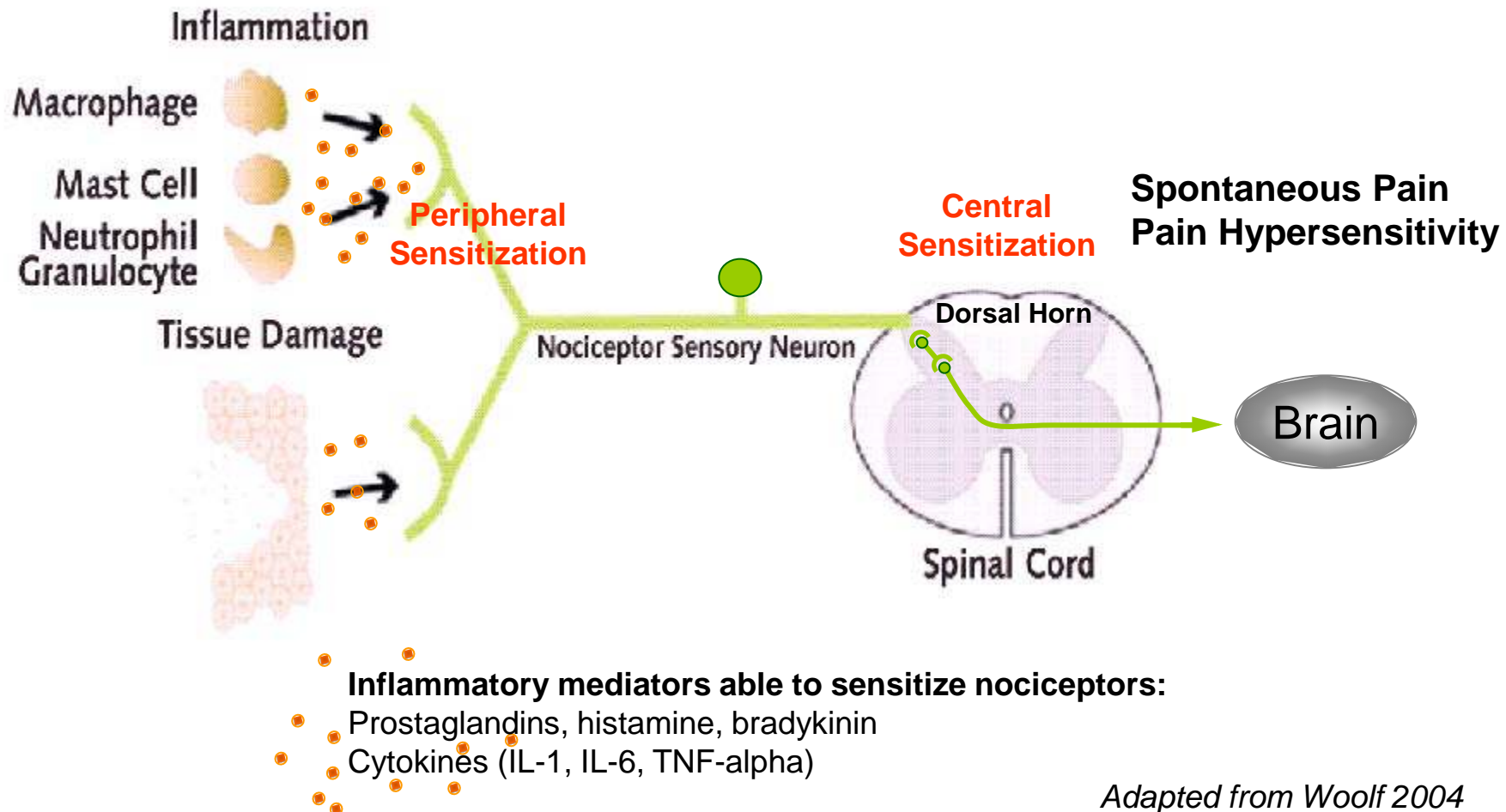
Ratings of single pain items



Potential mechanistic pathways

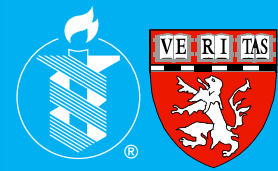


Inflammatory markers



Adapted from Woolf 2004

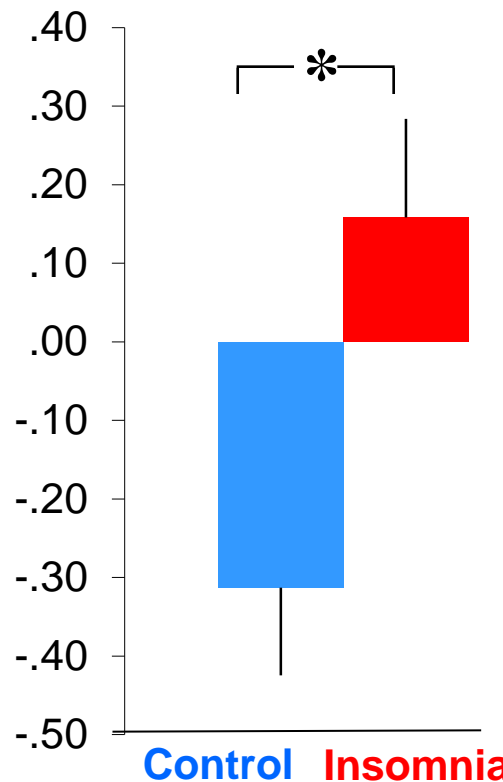
Inflammatory markers and pain reporting in insomnia disorder



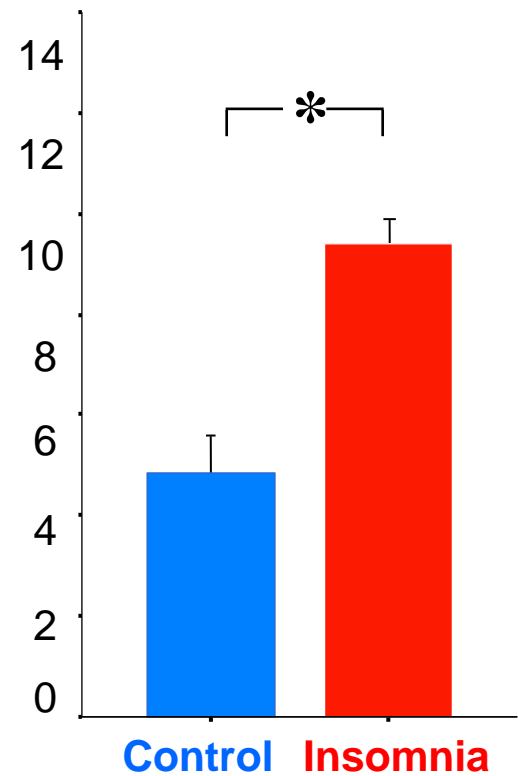
BIDMC - SLEEP STUDY
11" X 28" SUBWAY INTERIOR CARDS
BOSTON/METRA
SEPTEMBER 2003



Inflammatory Composite
(Z score IL-6, CRP, monocytes)

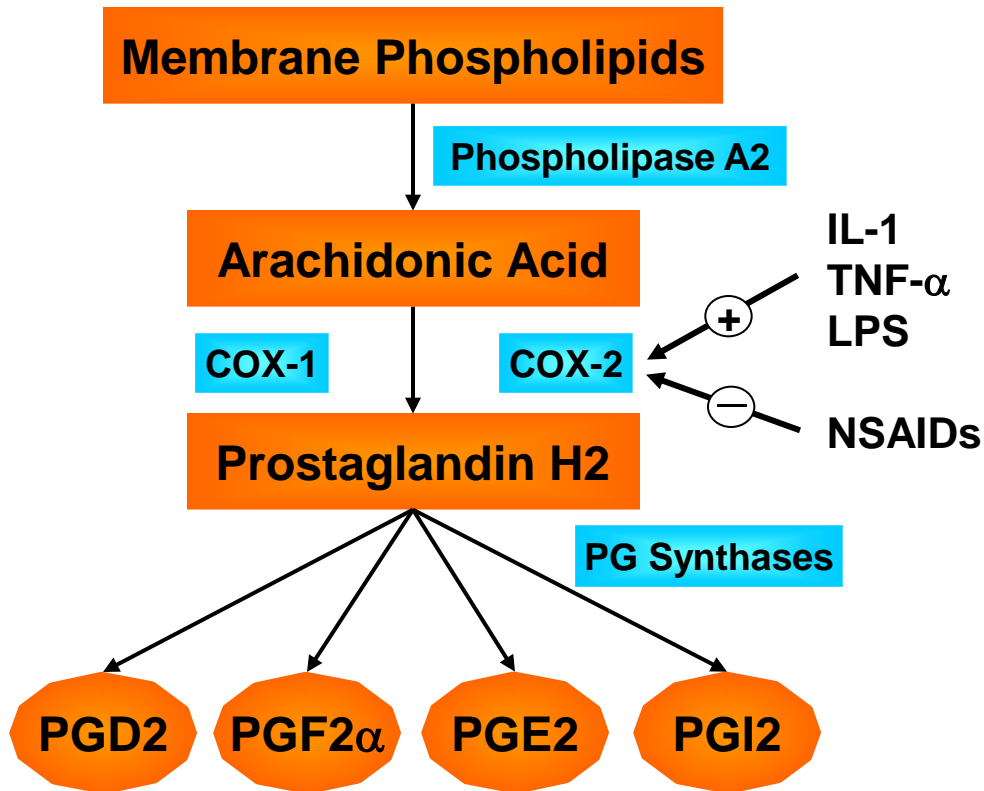
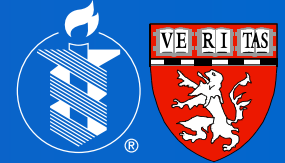


Pain Frequency (days)



N131 study data, manuscript in preparation

Prostaglandin (PG) System

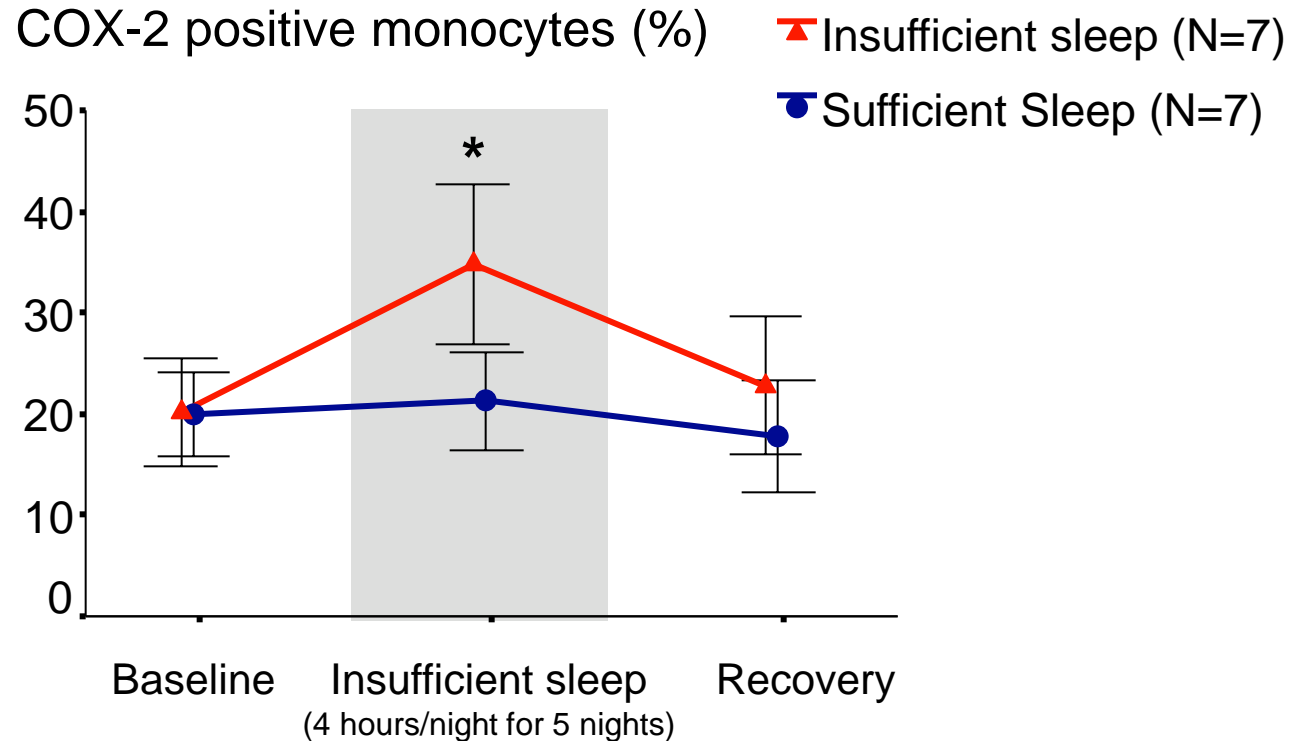
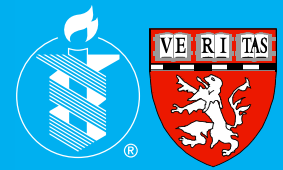


- PGs are involved in numerous homeostatic functions.

PGE2 appears to play a pivotal function in inflammation and pain.

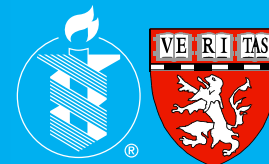
PGD2 has been shown to play a significant role in sleep-wake regulation.

COX-2 in response to insufficient sleep



Insufficient sleep in healthy, pain-free individuals increases the expression of COX-2 by monocytes.

Evoked pain in insomnia disorder: Participant Characteristics



Screening criteria

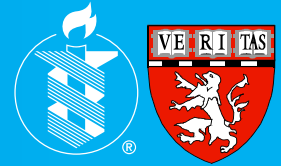
No current Axis I disorders (or history in last 6 months).

No current or past history of pain-related disorders.

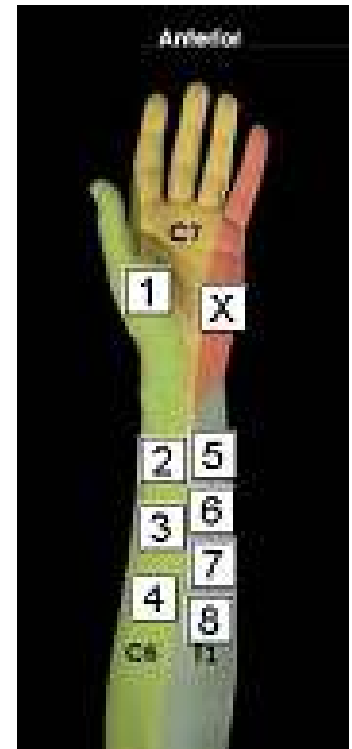
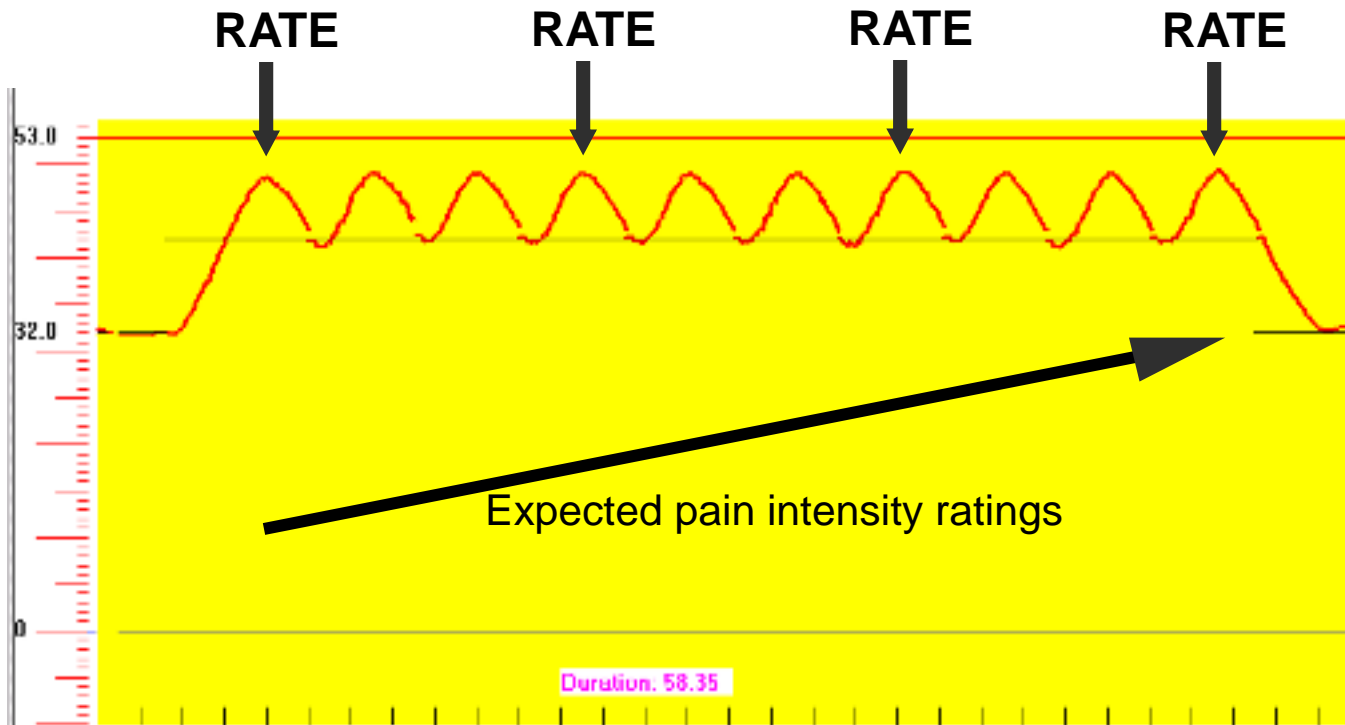
Free of any medication for >1month.

	Insomnia	Controls
Female/Male <i>Ratio</i>	11/6	11/6
Age (yrs) <i>Mean \pmSEM</i>	22.65 \pm 3.52	24.35 \pm 3.64
BMI <i>Mean \pmSEM</i>	23.27 \pm 2.90	22.14 \pm 3.51
Actual Sleep Time (actigraphy) <i>Mean \pmSEM</i> <i>Range</i>	6.08 \pm 1.11 3.50-7.37	6.82 \pm 1.03 4.47-8.12

Pain facilitation in insomnia disorder

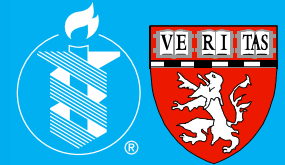


Test: Temporal summation of pain

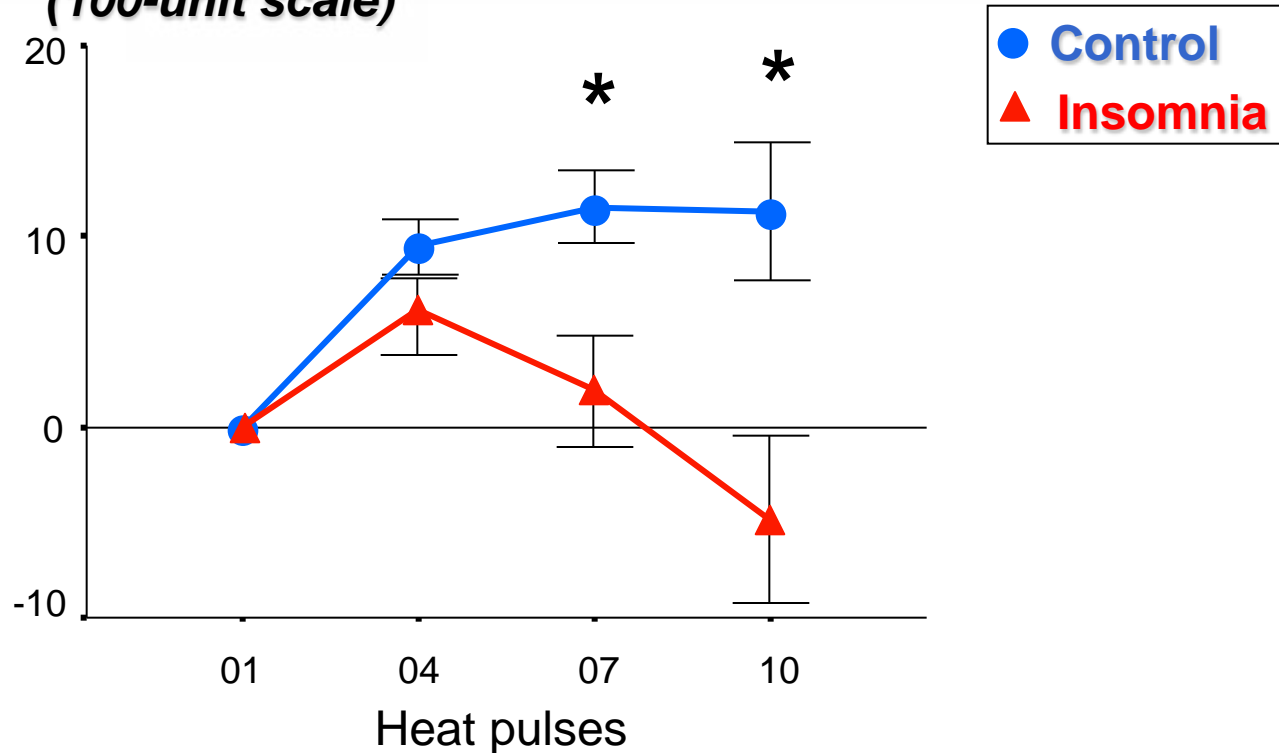


➤ Instruction: The temperature will rapidly increase and decrease. Rate the intensity of the sensation whenever I say 'RATE'.

Pain facilitation in insomnia disorder

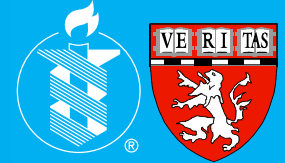


*Change of intensity ratings from baseline
(100-unit scale)*



Unexpectedly, individuals with insomnia disorder showed **less temporal summation** than controls. Due to active pain-inhibitory system resulting in quicker habituation to pain stimuli?

Pain inhibition in insomnia disorder



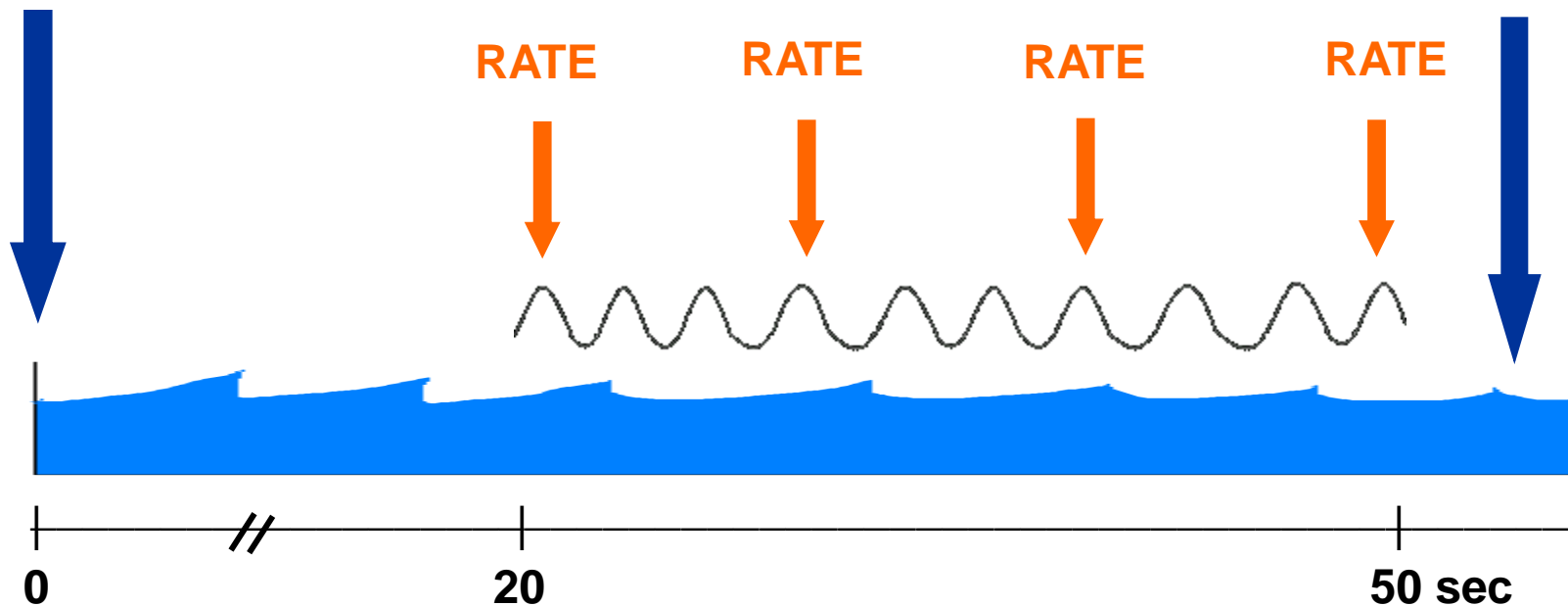
Test: Conditioned pain modulation (CPM)



Foot immersion
into 47°C water

Repeated heat pulses applied on forearm

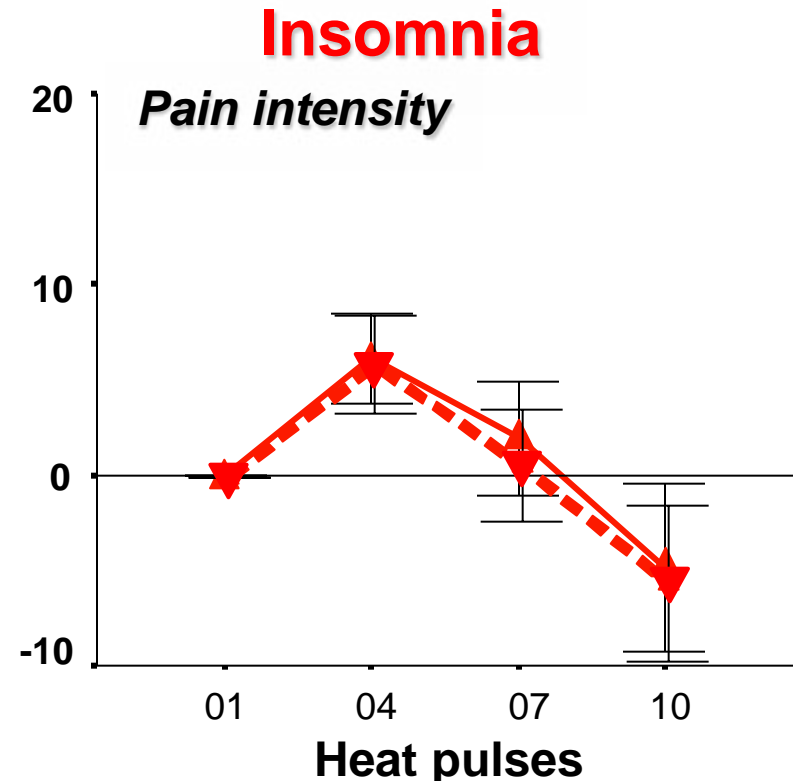
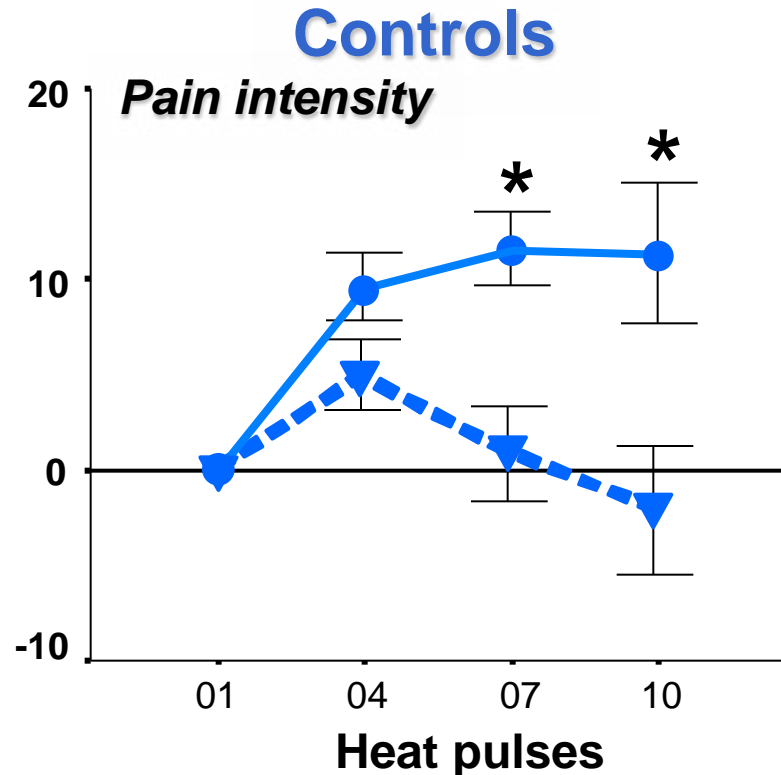
Foot removal



Instruction: While your foot is immersed in the water bath, I will ask you to rate the intensity of the heat sensation on your forearm....

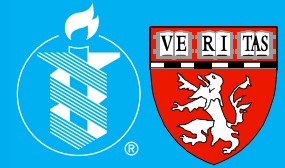
Pain Inhibition in insomnia disorder

— Baseline condition - - - Pain-inhibitory condition

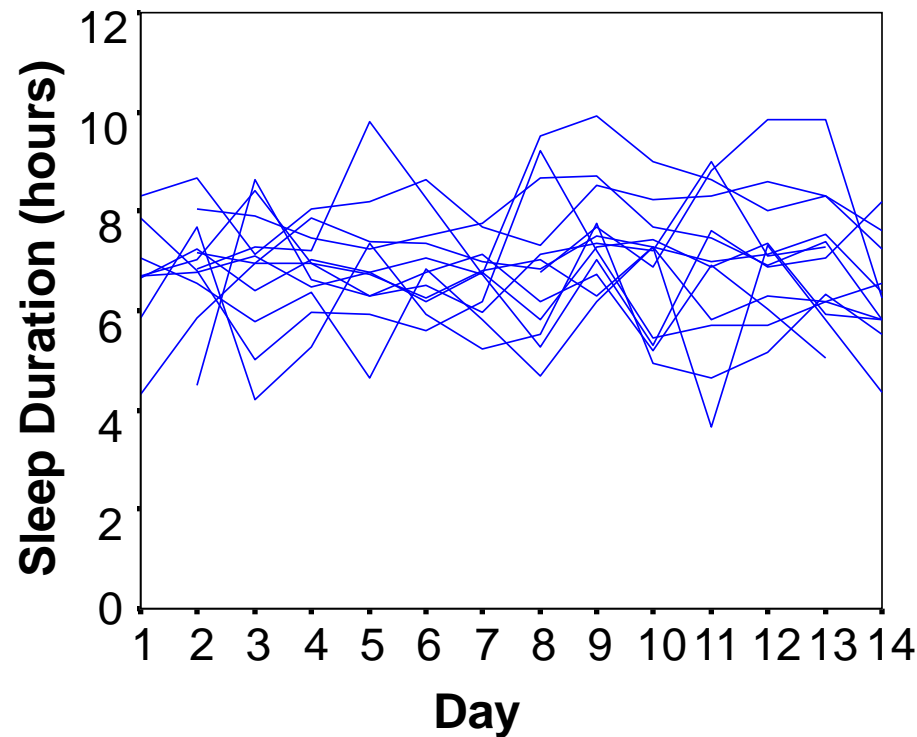


Capability to inhibit pain in the CPM test deteriorated in insomnia disorder.
Due to a constantly active pain-inhibitory system not able to respond to further challenge?

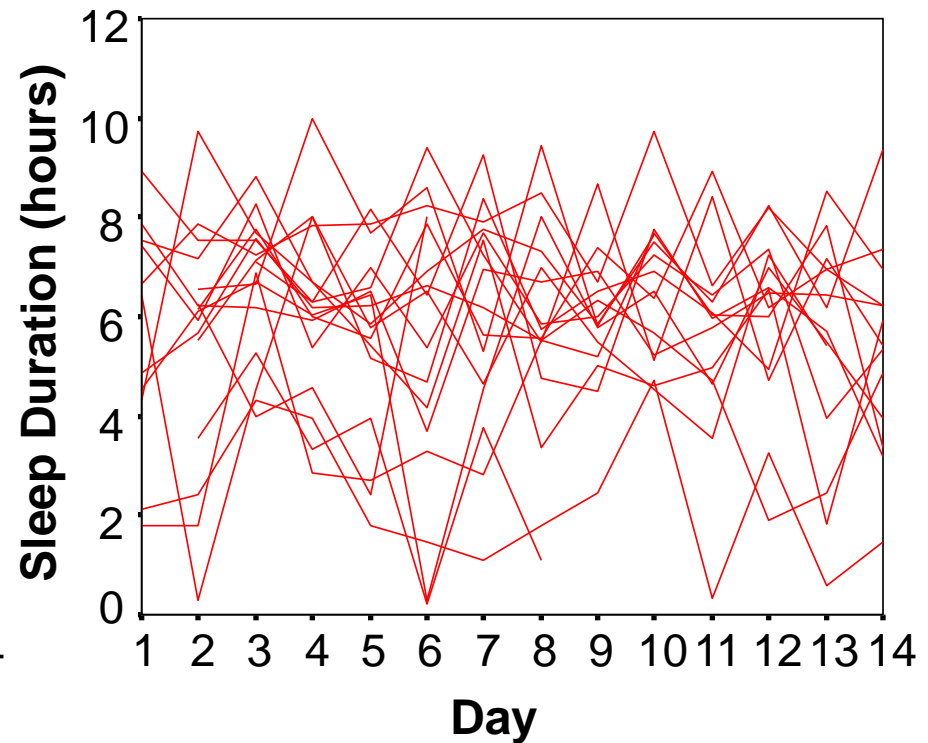
Day-to-day sleep duration in Insomnia disorder (actigraphy-based)



Controls

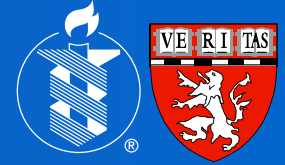


Insomnia disorder



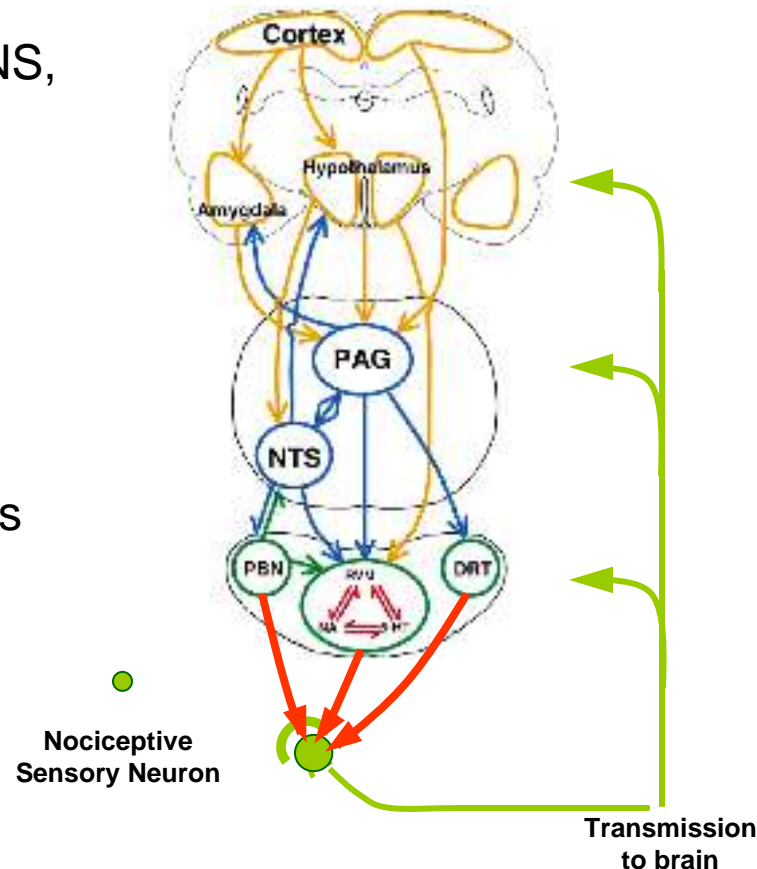
Low average, but also high variability of sleep duration in insomnia disorder.

Descending modulation of pain



- A noxious stimulus undergoes significant modulation in the CNS, i.e., it can be inhibited or facilitated, before the sensation reaches consciousness and is perceived.
- Triggers of pain inhibition:
 - Painful stimuli
 - Environmental dangers
 - Negative high-arousal emotions
 - Distraction/attention shift

Descending pain inhibitory pathways



Adapted from Millan, 2002